REMARKS

The Examiner's Office Action dated September 29, 2003 has been carefully reviewed. In view of the above amendments made to the claims and for the reasons provided below, early allowance of pending claims 1 to 19 is respectfully requested.

I. Claim Rejection: 35 USC § 103

The Examiner has rejected claims 1 to 19 under U.S.C. 103(a) as being unpatentable over Ho patent (USPN 5,109,117). However, the above 103(a) rejection is respectively traversed for the reasons provided below.

i) Summary of the present invention

By way of review, the present invention defined in pending claims 1 to 19, as amended, is directed to a process for the preparation of somatotropin from inclusion bodies which comprises solubilizing the inclusion bodies with an aqueous alcohol solution in the absence of a chaotropic agent, and refolding and oxidizing the solubilized somatotropin protein to yield active somatotropin.

ii) Summary of the Ho patent

In contrast, the Ho patent discloses a method for the solubilization and naturation of somatotropin from refractile bodies produced by r-DNA technology, wherein the refractile bodies are dissolved in an aqueous solution comprising a chaotropic agent such as urea and a soluble organic alcohol.

iii) Comparison of the present invention with the Ho patent

In spite of the Examiner's view, the inventive process is distinctly different from, and has numerous unexpected advantages, over the Ho patent's method.

The Ho patent cited by the Examiner has been acknowledged by the present inventors by including in Background of the Invention as a prior art, which discloses that the addition of a small amount of an alcohol to the solution containing a chaotropic agent enhances the solubilization and refolding rates (see page 2, lines 10 to 13, the present specification).

The critical feature of the inventive process is to employ only a water-soluble alcohol for solubilizing the somatotropin produced in the form of inclusion bodies without the use of a chaotropic agent such as urea. The inventive process employs an aqueous alcohol solution at a high concentration ranging from 10 to 50%. Such an aqueous alcohol acts to change the polarity of water to weaken the non-covalent attraction in the inclusion bodies and to offset the non-covalent attractions between the protein molecules.

While in the Ho patent, the role of the soluble organic alcohol used with a chaotropic agent such as urea is to suppress the formation of somatotropin dimmers and aggregates, resulting in higher yields of the desirable monomeric form of the protein.

Although the Ho patent discloses the use of a soluble organic alcohol for solubilizing the somatotropin, the Ho patent's method still requires a chaotropic agent as an essential component. A method which does not utilize a chaotropic agent for solubilizing the somatotropin as disclosed by the inventive process was not contemplated, described or implied by the Ho patent (see Abstract, Background at column 1, lines 22 et seq., Summary at column 2, lines 65 et seq., Description of Invention at column 3, lines 15 et seq., all Examples, and all the Claims).

More concretely, Examples of the present invention and the Ho patent are reviewed in detail as follow:

In Example 8 and Comparative Example 1 of the present invention, the renaturation yield of somatotropin purified by using a solution of a high alcohol concentration is nearly 100%, but the renaturation of somatotropin employing a chaotropic agent such as 4.5 M urea gives a yield of only 83.7%. Further, in Examples 1 and 2 which investigate the effect of an aqueous alcohol in the solubilizing step, it has been found that while the solubilization of somatotropin does not effectively occur at a low alcohol concentration, e.g., 10% n-propyl alcohol and 10% isopropyl alcohol, the somatotropin starts to be effectively solubilized at a alcohol concentration of 20% or more (see Figs. 1 and 2).

However, the Ho patent's method solubilizes the somatotropin in an aqueous solution comprising urea at a concentration of 3 to 4.5 M and a soluble organic alcohol ranging from 1 to 10%. Particularly, while the use of 3 M urea without the addition of a soluble organic alcohol in Example 2 shows 56% of refolding efficiency, the use of the mixture comprising 3 M urea and 1 to 5% isopropanol, 53 to 63% of refolding efficiency, respectively. From these results, the present inventors note that the addition of a soluble organic alcohol to the urea solution in an amount of from about 1 to 5% is effective for the solubilization and naturation process, but its synergistic effect is insignificant. Further, in Example 3, the refolding efficiency in case of using a mixture comprising 3 M urea and 3 to 5% benzyl alcohol becomes not higher but lower in the range of 63 to 10% than in case of using 3 M urea only. The Ho patent explains that a high level of benzyl alcohol has a negative effect on the refolding efficiency, probably as a consequence of the alcohol interfering with the ability of the protein to refold into its native conformation (see column 5, lines 6 to 11). Namely, although the Ho patent's method discloses the use of a minor amount of a soluble organic alcohol, since it has to employ a chaotropic agent such as urea with a soluble organic alcohol to efficiently solubilize the somatotropin, the Ho patent's method completely differs from the inventive process which employs only an aqueous alcohol solution at a high concentration

without the use of a chaotropic agent.

Further, while the Ho patent's method using a mixture of urea and a soluble organic alcohol takes several days for solubilizing the somatotropin (see Example 1 at column 4, lines 38 to 41 of the Ho patent), the inventive process using an aqueous alcohol solution takes only 5 to 30 min (see page 7, lines 17 to 21 of the present specification).

Consequently, the inventive process is advantageous over the Ho patent in that it is possible to obtain an active somatotropin at a high yield from the inclusion bodies produced in a recombinant host cell, without employing a chaotropic agent such as urea.

In view of the above, therefore, the Ho patent cannot possibly teach or render obvious the unique feature of the use of an aqueous solution having a high alcohol concentration without the use of a chaotropic agent or the beneficial effects arising therefrom.

On the other hand, the Examiner has noted that claims 1 to 19 are drawn to a product-by-process and stated that even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself.

In contrast to the Examiner's view, the applicants traverse this rejection. The pending claims 1 to19 of the present invention, all the claims in the case, are in the form of process claims, not product-by-process claims and thus, there is no antecedent factual basis for this rejection. The pending claim 1, the only independent claim in the application, reads "A process for the preparation of..." and the other claims list process steps. Therefore, it is the novelty and obviousness of applicant's process that is being claimed.

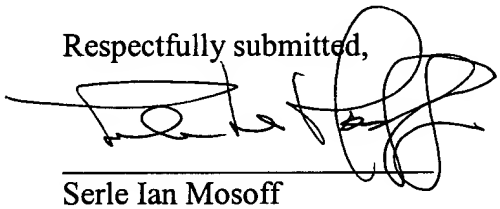
Accordingly, it is firmly believed that the present invention defined in claims 1 to 19 is clearly patentable and unobvious over the cited reference.

II. Conclusion

In view of the foregoing amendments and discussions, therefore, it is respectively submitted that the present invention as defined in the pending claims 1 to 19 is in full compliance with all the statutory requirements, and therefore, it is earnestly requested that the Examiner's rejections be withdrawn and the pending claims be allowed in their present form.

Any fee due with this paper, not fully covered by an enclosed check, may be charged on Deposit Account 50-1290.

Respectfully submitted,



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